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REVIEW ARTICLE

Contemporary Brachytherapy Approaches in Non–Small-Cell Lung Cancer

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Brachytherapy has the ability to deliver a higher tumor dose compared to external beam irradiation, while sparing normal tissue outside the tumor; it is the most effective means of delivering conformal radiation and can be tailored to clinical circumstances, either at open surgery or in an ambulatory setting, which is currently the preferred method. Intraoperative lung and/or endobronchial brachytherapy in the management of non–small-cell lung cancer offers a good curative potential in patients with accessible localized tumors, well defined and small to moderate in size, that have not metastasized to the lymph nodes and are technically or medically inoperable. Effective palliation can be frequently obtained by endobronchial brachytherapy on an outpatient procedure basis. Brachytherapy administered simultaneously with chemotherapy is better tolerated than a course of external beam irradiation and chemotherapy.

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INTRODUCTION

Since 1991 there is a significant downward trend in lung cancer incidence, seen among both men and women, and the number of deaths appear to be leveling off [1]. The American Cancer Society estimates that 171,500 new cases of lung cancer will be diagnosed in 1998, accounting for 13.5% of all cancer diagnoses. At the same time, an estimated 160,100 will die in 1998, accounting for 28.4% of all cancer deaths. Since 1987, however, more women have died each year of lung cancer than breast cancer, which, for over 40 years, was the major cause of cancer death in women. In 1998, lung cancer will account for 25% of all cancer deaths in women. Survival rates during the second half of this century have improved, but even by the best estimates only one out of eight lung cancer patients is expected to survive for 5 years.

The treatment of choice for operable non–small-cell lung cancer (NSCLC) is surgical resection. A small percentage of patients with NSCLC is suitable for curative radiation therapy. Local thoracic external beam irradiation, however, is limited by the tolerance of vital organs within the treatment area. The discovery of radium by Madame Curie 100 years ago created a new discipline of radiation oncology called brachytherapy. Brachytherapy, alone or in combination with external beam radiation or surgery, has been used effectively to improve local control. Brachytherapy is able to overcome many of the limitations of external beam radiation imposed by normal tissues.

The current trend for careful intraoperative staging and documentation of patterns of failures has generated information that is vital to the design of radiation therapy. For instance, it is clear today that the location and the size of the tumor will influence the pattern of failure and rate of survival. Patients with small tumors in the periphery of the lung have a lower incidence of locoregional

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recurrence and a better survival than patients with large tumors located near the hilum. Significant differences in frequency of local failures between patients with squamous cell carcinoma and those with adenocarcinoma or large-cell carcinoma have been also identified. The former have a higher incidence of local failures in both resectable and inoperable tumors [2].

BRACHYTHERAPY OVERVIEW

Intraoperative lung and/or endobronchial brachytherapy has a good curative potential in patients with localized small- to moderate-size NSCLC tumors that are well defined, have not metastasized to lymph nodes, and are easily accessible. Larger tumors, multiple lesions, or the presence of lymph node metastases preclude curative treatment by brachytherapy. In selected cases, however, quick and effective palliation may be obtained by an endobronchial outpatient brachytherapy procedure.

The theoretical advantages of brachytherapy can be summarized as follows: (1) it represents one of the most cost-effective means of delivering conformal radiation, requiring as a rule only one application; (2) it is easily adapted to tumor shape and size; (3) it delivers a higher tumor dose compared to external beam irradiation; (4) the delivered radiation dose decreases rapidly outside the treated tumor volume, significantly sparing the normal tissue in the tumor vicinity; and (5) it delivers the irradiation continuously over a long period of time, which, radiobiologically, is more effective than fractionated external beam.

Brachytherapy techniques and approaches can be tailored to the clinical situation and can be administered intraoperatively over a protracted time (low dose rate), or on an outpatient basis over a very short period of time (high dose rate). The treatment option to be used depends on the tumor location and the volume of gross disease. Discrete lung masses or mediastinal lymph nodes found to be unresectable may be treated at thoracotomy by a permanent implant, using Iodine-125 (I-125) or Palladium-103 (Pd-103) seeds. Unresectable chest wall lesions or microscopic disease at the margins of surgical resection may be treated intraoperatively by either a temporary Iridium-192 (Ir-192) implant or a permanent I-125 implant imbedded in absorbable polyglactin (vicryl) sutures and directly sutured onto the target area; or it may be treated by employing I-125 seeds imbedded into an absorbable gelatin sponge (Gelfoam) plaque [3]. Endobronchial tumors are managed either by a permanent I-125 or Pd-103 seed implant or more frequently today by an endobronchial remotely controlled Ir-192 high-dose-rate application.

Current areas under evaluation in lung cancer include exploring the value of video-assisted thoracoscopic brachytherapy and combining brachytherapy with other local therapies (external conformal radiation, laser beam) as well as systemic therapy (chemotherapy and immunotherapy).

INTRAOPERATIVE BRACHYTHERAPY IN NON–SMALL-CELL LUNG CANCER

Patients selected for intraoperative brachytherapy must have adequate pulmonary function in order to tolerate thoracotomy without major risk. They should also have NSCLC localized to the hemithorax without pleural invasion or pleural effusion and without evidence of distant metastases. The majority of the permanent interstitial implants of the lung are performed through a posterolateral approach, which is the usual approach when resection of a lung cancer is contemplated. This approach permits a good exposure of the tumor to be implanted and allows inspection of the hilar area and the ipsilateral mediastinum. It is unsatisfactory, however, for tumors extending to the contralateral hilum or mediastinum. A small anterior thoracotomy incision may be used in this instance, but the exposure is generally not adequate for effective implantation. The implantation time is short and does not add to the morbidity expected from thoracotomy alone [4].

RESULTS OF INTRAOPERATIVE BRACHYTHERAPY

Most reports on brachytherapy are retrospective and come from single institutions. The largest experience with intraoperative brachytherapy in lung cancer has been accumulated at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York. This nonrandomized intraoperative experience includes patients treated from the early 1960s through the mid-1980s and can be divided into three categories according to the stage of NSCLC.

Stage I and II Lung Cancer

There is in general a paucity of reports in the literature on the benefits of radiation therapy with curative intent in early lung cancer. We have published a retrospective analysis of 55 patients with stage I and II non–small-cell lung cancer who underwent thoracotomy but no resection because of severe cardiopulmonary problems, which rendered them unsuitable for resection but also unsuitable for radical external beam radiation [5]. These patients were treated at thoracotomy by interstitial I-125 implantation. Information obtained from bronchoscopy, thoracotomy, and postoperative pathology reports was used to define the stage of their cancer. There were no operative or postoperative deaths in this series of 55 patients. Following surgery, additional external beam was given in moderate doses to the mediastinum in 24 patients with hilar nodes or large primary tumors, carefully planned to avoid functioning lung parenchyma as much as possible. Locoregional control, at 5 years from treatment, was achieved in 100% (7/7) of patients with T1N0 lesions; in

70% (24/34) of patients with T2N0 lesions; and in 71% (10/14) of patients with T1-2N1 lesions. The difference was not statistically significant ($P = 0.48$). The overall 5-year survival rate was 32% and the disease-free survival rate 63%. The median survival was better in patients with cancer in the right lung (3.4 years) compared to those with cancer in the left lung (1.3 years); this difference was statistically significant ($P = 0.006$). No difference in survival could be demonstrated among patients with the two main histological subtypes of squamous vs. adenocarcinoma ($P = 0.78$); patients with T1 and T2 tumors ($P = 0.80$); and between patients who received postoperative external radiation and those who did not ($P = 0.62$). Surprisingly, the incidence of second primaries in this group of patients was only 9% (5/55).

Fleishman et al. [6] have recently published similar results with stage I medically inoperable patients treated with I-125 implantation at thoracotomy. With a minimum follow-up of 1 year, the local control was 71% and the median survival was 15 months.

Stage III Lung Cancer

Burt et al. [7] published the experience in patients with NSCLC invading the mediastinum (T3-4N0-2) who underwent thoracotomy at MSKCC and were treated by surgery supplemented by intraoperative brachytherapy when needed. When the data were analyzed by specific treatment modality, there was a positive correlation between prolongation of survival and extent of intraoperative therapy. Forty-nine patients who underwent complete resection of all intrathoracic disease had no long-term survival advantage and, in fact, did worse than 33 patients with incomplete resection and brachytherapy. The 2- and 3-year survival was 29% and 21%, respectively, with complete resection; and 30% and 22%, respectively, with incomplete resection and brachytherapy. At the same time, 101 patients who underwent brachytherapy only without resection had a 2-year survival of 21% and a 3-year survival of 9%. No impact of histological type was seen. The overall local control rate was 70%.

We have reported an earlier experience at MSKCC [8] regarding 322 patients with stage III NSCLC considered unresectable at thoracotomy and treated with brachytherapy. Local control was obtained in 71% of stage III patients with negative mediastinal nodes and 63% of patients with involved regional nodes. The 2- and 3-year survival with negative nodes was 20% and 15% vs. 10% and 3% in patients with involved nodes.

A subsequent group of 100 patients with NSCLC who had positive mediastinal nodes at thoracotomy were treated with a combined approach consisting of brachytherapy, surgical resection when feasible and postoperative external beam radiation [9,10]. Temporary Ir-192 implantation was performed in 55 patients with close or positive margins of resection in the superior mediastinum or the chest wall and permanent I-125 implantation in patients with residual gross disease. All patients received postoperative mediastinal irradiation to a median dose of 40 Gy 4 to 6 weeks after thoracotomy. This combined approach improved the local control from 63% in the earlier period to 76%. There was no postoperative mortality. Patients who had resection of all gross disease fared better than patients with incomplete or no resection. Local control for patients with no residual disease and brachytherapy was 77%, compared with 72% in patients who had gross residual disease and brachytherapy. The 5-year survival was 30% when complete resection of all gross disease was possible vs. 13% for patients who had incomplete or no resection and brachytherapy.

Superior Sulcus Tumors

This group of superior sulcus tumors (SST) merits a special consideration. SST is a locally invasive tumor usually with a reduced tendency for distant metastases. Patients with SST tend to come to the physician early because of pain. However, the pain is frequently attributed to cervical arthritis and disk disease, bursitis of the shoulder joint, or other benign neuromuscular conditions, resulting in long delays before a correct diagnosis is made. Prior to 1950, a superior sulcus tumor was considered uniformly fatal. The first cure, using interstitial brachytherapy, was reported by Binkley [11] in 1950. Shaw et al. [12] in 1961 advocated the use of preoperative radiation therapy routinely and recommended a dose of 3,000 cGy in 12 days, followed by an extended en bloc resection of the involved chest wall, intercostal nerves, portions of the first three thoracic vertebrae (including their transverse processes), stellate ganglion, and a portion of the sympathetic chain together with the affected lung. Subsequently, we reported the potential curative and palliative value of interstitial brachytherapy [13] either alone or in combination with preoperative external radiation [14,15]. We analyzed 129 consecutive patients with superior sulcus tumor who underwent thoracotomy at Memorial Sloan-Kettering Cancer Center. Whenever possible, en bloc excision of the involved lung and chest wall was carried out. A mediastinal lymph node dissection was also done to complete the removal of all diseased tissue and for further staging. Patients with unresectable tumors were treated by interstitial intraoperative brachytherapy, using either permanent implantation of I-125 seeds or temporary implantation of Ir-192. Postoperative radiation was given to patients who had received no preoperative radiation or to patients with unsatisfactory implant dose distribution. One of the 129 patients who underwent a thoracotomy died within 30 days after operation of pulmonary embolism (0.8%); and 17 patients (13%) developed nonfatal complications. These included wound infection in three patients, empyema with

or without bronchopleural fistula in four, bleeding in three, atelectasis or pneumonia in six, and phlebitis in one. There was no evidence of any adverse effect from the moderate dose of preoperative radiation therapy given in 82 of the 129 patients. The only radiation toxicity encountered was mild transient dysphagia. The limiting factors for surgical treatment of SST were invasion of the spine, involvement of the major vessels, and extension to involve the upper rami of the brachial plexus.

The overall 5-year survival was 25%. Patients with adenocarcinoma had a better 5-year survival than patients with squamous cell carcinoma: 30% and 19%, respectively. Patients with negative mediastinal nodes did better than patients with positive nodes, with a 5-year survival of 29% and 10%, respectively. The 5-year survival was improved when preoperative irradiation was administered (29%) than when it was not (20%).

Prospective Randomized Trials in NSCLC

In the 1980s, a prospective randomized trial was conducted at MSKCC to determine whether adjuvant postoperative chemotherapy with vindesine and cisplatin would lengthen the disease-free interval and prolong survival in patients with surgically documented positive nodes treated with surgery or brachytherapy or both, and followed by postoperative external beam irradiation. Pisters et al. [16] in 1994 reported the final results of this prospective randomized study. A total of 72 patients were entered and 36 were randomized to receive chemotherapy. Twenty of 28 patients with incomplete resection were treated by permanent I-125 brachytherapy (10 patients in each arm); the remaining 8 patients were not suitable for implantation. At 2 years, 70% of the patients treated with radiation alone had progressed, compared with 89% of the patients treated with both radiation and chemotherapy; and at 5 years, 78% and 89%, respectively. The median survival was 19.1 months for radiation alone and 16.3 months for radiation and chemotherapy. The 2- and 5-year survival for radiation alone was 44% and 30% vs. 31% and 17% for radiation and chemotherapy. There was no difference in overall recurrence rate, local recurrence rate, or the incidence of systemic recurrence between the two treatment arms. There was no difference in toxicity, which was very mild. Furthermore, the simultaneous administration of chemotherapy and brachytherapy was extremely well tolerated with no noticeable increased toxicity. This experience has shown that adjuvant chemotherapy with the given dose and schedule of vindesine and cisplatin does not prolong the disease-free interval or survival in patients with locally advanced non–small-cell lung cancer treated with resection or brachytherapy and mediastinal irradiation.

Armstrong et al. [17] reported preliminary results of a prospective phase II trial of aggressive induction chemotherapy, surgical resection, selective intraoperative brachytherapy, and postoperative external beam radiation for patients with NSCLC and involved mediastinal nodes. Of the 41 patients initially entered, 30 responded to chemotherapy; 28/30 responders and 6/11 with minimal or no response underwent thoracotomy. Intraoperative brachytherapy for residual disease was performed in 10 patients. In spite of the advanced disease in the brachytherapy group, actuarial progression-free survival at 2 years and 5 years was 66% and 55%, respectively.

A critical review of the long-term results of intraoperative low-dose-rate lung brachytherapy alone or in combination with other local and systemic therapies suggests that a variable proportion of patients with gross or microscopic disease left in the thorax after incomplete resection or biopsy only can be controlled locally. Brachytherapy may contribute to a long-term survival in some of these patients. This approach is especially beneficial for selected patients with early disease and limited pulmonary reserve who cannot tolerate resection, and for patients with apical peripheral lesions. The close working relationship between radiation and surgical oncologists permits a more accurate intraoperative assessment of the tumor and a more effective combined therapy. The effects of intraoperative brachytherapy alone on pulmonary function, in comparison with those of external beam radiation, suggest a significantly decreased incidence of pulmonary fibrosis.

ENDOBRONCHIAL BRACHYTHERAPY

Endobronchial tumors present a difficult therapeutic problem. Most often these patients have primary NSCLC and present with endobronchial disease following a definitive course of surgery and/or external beam irradiation. The most common methods of treatment include endobronchial excision of tumor or laser coagulation. The improvement obtained from these procedures is usually limited to 3 or 4 months, and repeated treatments become more difficult and less effective. In recent years, there has been a rapid increase in the use of endobronchial brachytherapy to treat endobronchial recurrence or as part of the initial treatment for primary NSCLC. Two technological developments have led to the increased utilization of endobronchial brachytherapy. The first is the introduction of high-dose-rate (HDR) remote afterloading brachytherapy permitting treatment on an outpatient basis with reduced exposure to personnel. The second major development is the advent of fiberoptic bronchoscopy and its widespread utilization, which allows the insertion of small-caliber afterloading catheters in every major branch of the tracheobronchial tree, even in critically ill patients.

Endobronchial brachytherapy is often used for palliative purposes in patients with recurrent endobronchial disease after prior external irradiation, to relieve life-

threatening complications, such as hemoptysis and airway obstruction with an associated atelectasis and pneumonia. Endobronchial brachytherapy is less frequently used in combination with external beam irradiation to deliver an additional ''boost'' with curative intent to the primary endobronchial lesion in patients with poor lung function precluding surgical resection. The technique is relatively simple and can be performed in the ambulatory setting. Patients, however, must be continually monitored in terms of pulse, blood pressure, pulse oxymetry, and electrocardiogram (ECG) at frequent intervals. After adequate sedation and airway anesthesia, the bronchoscope is introduced, the tumor is visualized, and the distance between the proximal and the distal end of the tumor is measured. Both sides of the tracheobronchial tree are inspected to determine whether one or more catheters will be necessary, and the catheter(s) placement is carried out through the accessory port of the bronchoscope past the obstruction. The placement is confirmed visually and fluoroscopically and the bronchoscope is withdrawn without disturbing the catheter position. The catheter is then secured at the nose. The treatment is fast, efficient, and technically easy [18]. Treatment time, usually less than 15 minutes, depends on the activity of the Ir-192 source, length of tumor, prescription point, and prescribed dose. Treatments may be repeated several times.

Today, powerful computers with graphic capabilities combined with computerized tomography and/or magnetic resonance imaging make it possible to incorporate three-dimensional dosimetry information superimposed to anatomical structures.

HDR ENDOBRONCIAL BRACHYTHERAPY RESULTS IN NSCLC

There are now numerous studies in the literature that support the use of endobronchial HDR brachytherapy to palliate local symptoms, such as cough, dyspnea, and hemoptysis. Overall response rates (clinical, radiologic, and bronchoscopic), reported in over 1,000 patients treated with HDR endobronchial brachytherapy, are in the range of 80%–90%, with most cases considered a complete response [19,20]. Hemoptysis appears to be particularly responsive. Cough and dyspnea can be palliated in more than 50% of cases. The effectiveness of treatment depends on a number of factors, with radiation dose being the most important. Doses higher than 1,000 cGy at 1 cm from the source may give slightly better response rates but at the cost of increased morbidity, especially fatal hemoptysis. Similar results were subsequently reported by Taulelle et al. [21] and Hennequin et al. [22].

Gollins et al. [23] has recently reported one of the largest series of patients treated with HDR endobronchial brachytherapy at the Christie Hospital in Manchester. Four hundred and six patients with primary NSCLC and endobronchial disease were treated with endobronchial irradiation as the initial treatment (324 patients); or following external beam and presenting with an endobronchial recurrence (65 patients); or as an initial combined external beam and endobronchial radiation (17 patients). Patients were treated with a single application delivering at 1 cm from the central axis of the source 20 Gy (18.5%), 15 Gy (79.6%), or 10–14 Gy (the remaining 1.9%). Treatment morbidity was assessed at various intervals after HDR treatment. The most common early side effect was a transient exacerbation of cough resolving within 2–3 weeks. Complete tumor resolution was observed in 65% of 83 patients undergoing bronchoscopy within 3 months after treatment. In 46% of the 83 bronchoscopies, various degrees of radiation reaction was observed, resulting after 6 months to fibrosis. Radiation reactions were seen more frequently after 20 Gy than after 15 Gy or less. Fatal hemoptysis was determined as the cause of death in 32/406 patients. Multivariate analysis identified as risk factors a dose of 20 Gy, a prior laser therapy at the site of HDR application, and a second HDR treatment at the same site as the first treatment. It was further determined that in 20/25 (80%) assessable patients with fatal hemoptysis, there was evidence of residual or recurrent tumor before death, while in the remaining 5/25 patients there was none. It was also determined that most of these deaths occurred between 9 and 12 months after treatment, in contrast to deaths from other causes where the peak was between 3 and 6 months.

Huber et al. [24] reported the results of a prospective randomized study in which 42 patients with unresectable NSCLC were treated with external beam alone (60 Gy) and were compared with 56 patients treated with an additional boost of HDR brachytherapy, of 4.8 Gy each, before and after external beam radiation. There was no statistically significant difference in survival between the two groups (median survival 28 weeks and 27 weeks, respectively). Local control was increased in all patients who received HDR boost with borderline significance ($P = 0.052$); this difference was, however, statistically significant in patients with squamous cell carcinoma ($P = 0.007$). The median duration of response was 12 weeks without HDR boost vs. 21 weeks with boost. Fatal hemoptysis was the cause of death in 6 of 42 patients in the first group and 11 of 56 patients in the second group; this difference is not statistically significant ($P = 0.22$). Survival time of patients with hemoptysis as the cause of death was similar within the two groups (median survival 23 weeks without boost vs. 26 weeks with boost). The authors concluded that there seems to be an advantage in survival time, although not statistically significant, for patients treated with a brachytherapy boost.

Ornadel et al. [25] have recently reported a prospective analysis of symptom response, duration of response, and

prognostic factors in 117 patients treated with brachytherapy at the Middlesex and Whittington Hospitals in London. With one exception, all of the patients had recurrent disease after prior external beam radiation therapy. A dose of 15 Gy was delivered in a single fraction, at a distance of 1 cm from the central axis of the catheter. Pretreatment symptom scores were recorded; dyspnea was the predominant symptom, with at least some restriction of exercise tolerance in two-thirds of the patients. In each case the proportion of patients reporting improved symptoms is higher after treatment. At 3 months after treatment, 77% of patients with initial cough had only minor or no cough; 73% of patients with dyspnea had no or minimal dyspnea; 89% of the patients with hemoptysis had no further symptoms on follow-up; and 84% of the patients recorded an improvement of performance status. The mean times to progression for each symptom, for those with symptom deterioration, was cough 6.8 months, dyspnea 4.2 months, and hemoptysis 5.5 months. An actuarial risk of fatal hemoptysis of 11% at 1 year and 20% at 2 years was associated with prior laser resection. There was no correlation between total dose of prior external beam irradiation and fatal hemoptysis. The median survival was 12 months. The authors are currently conducting a randomized study to test the value of endobronchial brachytherapy following laser resection to prolong the duration of symptom relief, although recognized the increased risk of fatal hemoptysis. The United Kingdom Medical Research Council study LU18 is currently addressing the relative efficacy of endobronchial techniques (including laser, cryotherapy, and brachytherapy) combined with external beam radiation in previously nonirradiated patients [25].

The analysis of all these reports and numerous others in the literature suggests that HDR endobronchial irradiation can provide significant palliation of severe symptoms caused by primary or recurrent endobronchial disease. Patient condition, tumor extent, and aggressiveness of HDR therapy have obvious effects on the incidence of morbidity. The optimal approach, however, remains unclear, especially in terms of dose per fraction and number of fractions. We believe that no more than 10 Gy, prescribed to a depth of 1 cm from the central axis of the source, should be given in a single application. In debilitated patients or patients who have previously received large doses of external beam irradiation, a dose of 5 Gy per application is recommended. We feel that when HDR is available, it is the preferred method of treatment because of advantages in patient comfort, convenience, and safety. Until more is known about mucosal tolerance, we choose to be conservative with fraction size and prescription point. Further randomized studies are clearly needed to answer these questions.

CONCLUSION

Aggressive, carefully planned brachytherapy of the primary NSCLC is capable of controlling tumor locally and, short of surgery, remains a most effective local agent in the management of NSCLC. Not surprisingly, the use of single-modality local therapy or combined-modality local therapies does not have a major impact on survival, because many of these patients will fail of metastatic disease either to the brain alone or to other sites. More effort is therefore needed to develop innovative combinations of systemic and local treatments. In our eagerness to improve the outcome of these patients, we should not overlook the local treatment in search of better systemic treatment. Furthermore, the subsequent symptoms of local intrathoracic recurrence require treatment when they occur. An argument in favor of brachytherapy as a single-modality or as component of multimodality therapy, in addition to its effectiveness, can be made today because of less cost and less expenditure of time for outpatient treatment.

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